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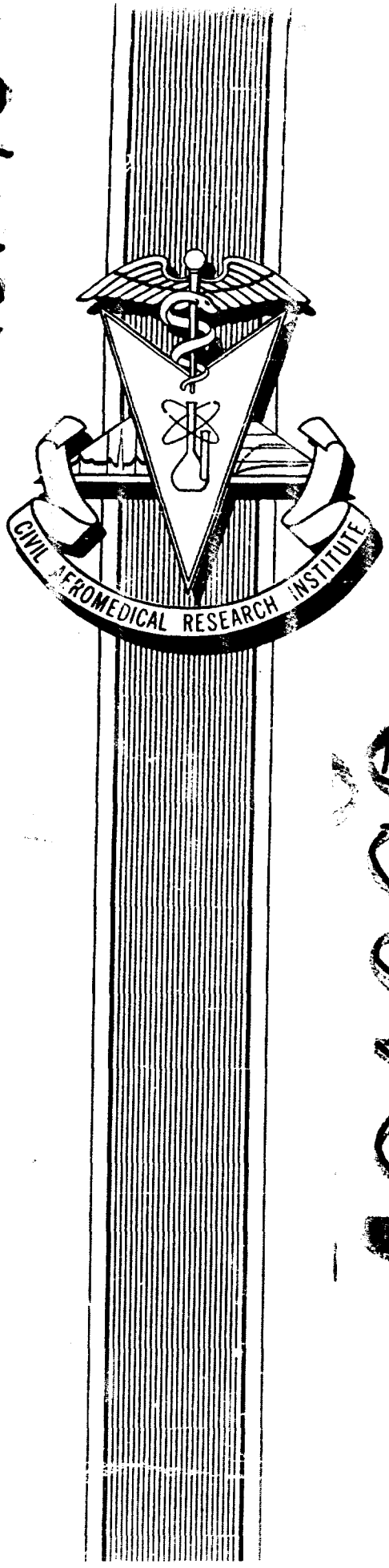

CENTRAL NERVOUS SYSTEM EFFECTS OF CHRONIC EXPOSURE TO ORGANOPHOSPHATE INSECTICIDES

63-24

FEDERAL AVIATION AGENCY
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OKLAHOMA CITY, OKLAHOMA

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The organophosphate cholinesterase-inhibitors, which were first introduced during World War II as potential agents of chemical warfare, have yielded a variety of derivatives which are now among the most widely used of all pest-control agents.

As early as 1941 it had been established that the high toxicity of these compounds was due to the persistence of their anticholinesterase action, although the mechanism by which they inactivated the enzyme was not known until later. Certain of these compounds are still used in the treatment of such clinical states as glaucoma and myasthenia gravis, where persistence of action can be an advantageous feature.

While the symptoms of organophosphate poisoning vary in rapidity of onset, severity and duration depending on the specific compound involved and a variety of other factors, they are readily divided into two categories, peripheral and central, depending upon their point of origin.

The peripheral symptoms are, in general, more dramatic and immediately incapacitating than are the central effects, and until about ten years ago the latter had received little attention. At about that time it began to be realized that cholinesterase inhibitors could produce sensorimotor, behavioral and personality changes, but there was no general agreement as to their potential severity and importance.[1]

Little has been written about this problem in the intervening years, but recent reports, particularly that of Gershon and Shaw,[3] have firmly established the psychiatric sequelae of organophosphate poisoning as a toxicologic entity. Moreover, although the patients in these studies were ultimately considered to have recovered completely, it is now apparent that this group of chemicals is capable of causing reversible symptoms of surprisingly long duration.

We have recently encountered two cases, both aerial-applicator pilots, who present the typical complex of such psychiatric symptoms. There seems to be little doubt of the casual relationship between exposure to organophosphate pesticides and their behavioral changes. Both cases are considered to be of special interest because of the long duration of their symptoms after their last contact with agricultural chemicals.

REPORT OF CASES

Case #1.

At the time of his physical examination for a Federal Aviation Agency second class medical certificate, a 35 year old farmer-pilot with 4775 flying hours revealed a history of previous treatment for a psychiatric condition. Because a diagnosis of psychosis had at one time been made, he was denied certification under Section 29.3 (d) (i) (ii) of Part 29 of the Civil Air Regulations (now Section 67.15 (d) (i) (ii) of the Federal Aviation Regulations). A current psychiatric evaluation was obtained and accompanied his appeal to the Civil Air Surgeon for reconsideration.

Review of the record revealed that he had undergone eight months of psychotherapy for an anxiety reaction with tension headaches 3½ years prior to this examination. Just prior to this treatment, he had failed to accept realistically the death of his 93 year old father and was greatly upset when one of his children ingested a foreign body one month later. He was actively engaged in the aerial application of organophosphate insecticides immediately preceding and during this treatment. When little improvement occurred he was hospitalized with a diagnosis of a neurotic reaction with obsessive compulsive, phobic and depressive symptoms.

At the time of admission he complained of angina and was unable to work despite the assurance of physicians that no disease existed; he was fearful of being alone, depressed, and despondent with crying spells. He had no suicidal impulses, insomnia, ideas of guilt or punishment, or depersonalization. The past medical history, family history, and physical examination were not significant.

Laboratory studies were as follows: hematocrit, 43 per cent; hemoglobin, 15.4 gm.; white blood count, 7,700, with normal differential; BUN, 10.3 mg. per cent; fasting glucose, 114 mg. per cent; total serum proteins, 7.60 gm. per cent; albumin, 4.27 gm. per cent globulin, 3.33 gm. per cent; alkaline phosphatase, 3.3 units; bromsulfalein test, 12 per cent retention in 45 min.; cephalin flocculation, 24 hrs.: 2+, 48 hrs.: 2+; prothrombin time, 80 per cent activity; Kline, negative. No cholinesterase determination was performed.

Baseline and double Master's test electrocardiograms were normal. No electroencephalogram was performed.

A chest x-ray was normal as were upper and lower gastrointestinal series and oral cholecystography.

He received 19 electroshock treatments and was discharged after two months on iproniazid, 35 mgs. daily, and pyridoxine, 150 mgs. daily. The final diagnosis was psychotic depressive reaction.

This hospitalization was not reported until the third annual physical examination for a second class medical certificate following discharge. At this time he denied any commercial flying during the two years immediately following his hospitalization. He reported 600 hours flying time in the preceding year and denied any symptoms referable to the nervous system.

The medical record including the current psychiatric evaluation was reviewed by the Civil Air Surgeon's Medical Review Board. Since there was no disqualifying physical defect present at this time and since the correct diagnosis may have been that of "acute brain syndrome probably resulting from exposure to toxic chemicals," a medical certificate was issued with the stipulation that a current psychiatric evaluation be obtained at the time of his examination for renewal of his medical certificate.

Case #2.

A 37 year old Latin American agricultural pilot visited CARI in February 1963 seeking help for recurrent bouts of acute anxiety, which he believed to have resulted from long exposure to organophosphate insecticides.

He began aerial application in Texas ten years ago after serving ten years as a pilot in the Chilean Air Force. One year later he moved to Guatemala where he still resides. Review of his role as an owner-operator reveals the use of a wide variety of aircraft to spray mostly cotton with methylparathion, DDT, toxaphene, endrin, and dieldrin. The normal season is from July through December; the normal workday is from 6:00 a.m. to 2:00 p.m., five to seven days a week depending upon the weather. The farmer selects and purchases the insecticide and furnishes the landing strip and mixing facilities. The owner-operator employs a mixer and a flagman and, when business warrants, may employ a second pilot. The pilot usually helps with the mixing about every third day. The insecticide mixture for each of the 30 to 50 daily flights is loaded in 1½ minutes from an overhead tank. Spillage is common and results in discoloration of the left wing and the ground. Review of his personal habits revealed that he cleaned his plane, inside and out, at the end of each day and wore a respirator in which he changed the filters every day and the cartridge every two or three days.

In January 1955 he began applying a mixture of methylparathion and DDT on a plantation in Peru. The living quarters were quite near the mixing and loading area and the odor of insecticide was said to be constant. He reported that nausea and diarrhea were prevalent among the twenty pilots employed. In March he sought medical advice, was told that he had liver and kidney damage and was advised to stop spraying.

He resumed spraying in July 1955. During the next six seasons he experienced gastrointestinal complaints about every ten days. He reported that this is a common experience of aerial applicators in his country and that the use of a mixture of atropine, sugar and charcoal for relief of symptoms is widespread. During 1957 he sought medical advice for nausea, chills, and tightness in the chest. He was advised to rest a few days before he returned to flying.

On September 26, 1961, his clothing was saturated with a mixture containing methylparathion, toxaphene and Dipterex when the tank of his aircraft was accidently overfilled. He washed his face, shoulders and hands and continued flying. Three trips later he was "too sick to fly" with nausea, abdominal cramps, dizziness, chest tightness, extreme weakness of hands and legs, and a rash on his wrists. He was hospitalized for five days. He reports that his cholinesterase was 20%, his liver was enlarged and liver tests were "abnormal." His ability to stand erect with his eyes closed was tested daily; he consistently fell to the left until the sixth day, he day he was discharged. He became nauseated and dizzy in a nearby restaurant. This led to another cholinestrase determination which he was told showed 12% activity. The following day he returned to flying but experienced a recurrence of symptoms on the third day. He was advised against further aerial application and received social security for the next six months (through March 1962). An EEG obtained in January 1962 appeared to be normal although he experienced dizziness during photic stimulation.

In May 1962 he was re-evaluated. At this time his cephalin flocculation was + (48 hrs.), his thymol turbidity was 3 units, and his bromsulfalein was 5.5% retention after 45 minutes.

He returned to aerial application in July intending to work only two days per week. He experienced nausea and weakness on the second day and went to the hospital outpatient department where he was given the mixture of atropine, sugar and charcoal. En route home he experienced dizziness. He returned to the hospital and obtained a blood count which he reports showed 11,500 WBCs per cubic millimeter. He was denied any medical support for further social security benefits. He was informed that a tonsillitis could be responsible for the elevated white count; he, therefore, underwent a tonsillectomy. After recovery he attempted a return to working one day per week but experienced the same symptoms. He stopped work in late August 1962.

At the time of his examination here his chief complaint was of recurring episodes of acute anxiety. His usual geniality has been marred by sudden outbursts of temper the past two years. He feels "closed in" and experiences sweating and difficulty breathing when alone in a car or airplane. On one trip he had to land because of his symptoms. While he once enjoyed flying at altitudes up to 12,000 feet, he now becomes symptomatic above 5,000 feet. He is symptom-free in the presence of another person, even a non-pilot. Ingestion of alcohol is also noted to relieve his symptoms. He admits fear of being alone in a closed space as a child but denies any recurrence of these symptoms until the past two years. He is now extremely sensitive to the odor of even low concentrations of chemicals and experiences nausea and chest tightness when he smells benzene, gasoline, ether, or similar compounds.

The past medical history is non-contributory except for an uncomplicated appendectomy at age 20. The family history and review of systems are similarly non-contributory. There were no abnormal findings on physical examination.

Laboratory studies were as follows: red blood count, 5,340,000 per cubic millimeter; hematocrit, 52 per cent; hemoglobin, 17.2 gm.; white blood count, 7,100 with normal differential; total cholesterol (non-fasting), 318 mg. per cent; thymol turbidity (non-fasting), 5.2 units; urinalysis, normal.

A chest x-ray and an electrocardiogram were normal.

An electroencephalogram showed paroxysmal 5-7 per second slow waves (theta waves) of approximately 50 microvolts present most prominently in leads Fp_1, Fp_2, C_3, and C_4; less prominently in leads O_1, O_2, T_3, and T_4; and absent in lead T_7 and T_8. Occasional high voltage bursts (above 100 μV) appear in leads Fp_1, Fp_2, C_3, and C_4. There were no significant changes with hyperventilation and photostimulation.

DISCUSSION

It is commonly accepted that the toxic actions of the organophosphate pesticides result from their inhibition of the cholinesterase enzyme. Unlike the carbamates and a variety of other chemicals and drugs which exert a temporary or transient effect on the activity of this enzyme, the organophosphates exert a persistent action because of the formation of a chemical bond between the phosphorus-containing radical and a receptor site on the enzyme itself. The rate at which phosphorylation takes place following contact between organophosphate and enzyme varies from compound to compound, as does the firmness of the bond. The rate of this reaction, along with many other factors such as size of dose, route of exposure, enzymatic transformation of the toxic material in animal tissues, and the rate of excretion, contributes to the rate of depression of cholinesterase activity and the time of onset and severity of such symptoms as occur. The firmness of the phospate bond is the controlling factor in determining whether some spontaneous reactivation of cholinesterase can occur or whether recovery of full activity depends entirely on *de novo* synthesis of a new complement of enzyme.

The firmness of the bond increases with time, and this factor greatly influences the success of efforts to reactivate the enzyme by means of 2-PAM or other, similar antidotes.

Following a single, massive dose of an organophosphate compound given orally or parenterally, the activity of plasma (pseudo) cholinesterase can fall to near zero in one hour, and that of red cell (true) cholinesterase will reach a similar level in two hours. The red cell activity is believed roughly to parallel that in nerve, muscle and gland. A rapid fall of enzyme activity usually coincides with a rapid onset of acute symptoms. Following a single exposure, recovery of from 13% to 19% of the pre-existing enzyme activity can occur within 24 hours. Plasma activity thereafter returns to normal in 30 to 40 days, and the erythrocyte level in about 90 days.

A considerable lack of precision is inherent in the methods most commonly used for routine measurement of cholinesterase activity. Therefore the values of 20% and 12% reported by the second pilot as having been obtained in that sequence, five or six days apart, do not necessarily indicate a real decrease in activity during this period, especially since the determinations seem to have been made in different laboratories.

The peripheral autonomic and somatic motor responses to acutely toxic doses of organophosphates are in actuality, therefore, the responses of these systems to accumulated acetylcholine. Generally, the responses correspond to the predictable effects of systemically administered acetylcholine, the differences being primarily quantitative, but there may be exceptions. While the heart is usually slowed by acetylcholine, organophosphates may cause acceleration with palpitation and discomfort in the precordial region instead. This may be due to nausea sufficient to overcome the expected bradycardia, or to stimulation of the adrenal glands resulting in release of catecholamines. Dilation of the pupil may occur instead of the predictable myosis.

A more detailed account of the symptomatology of organophosphate poisoning is to be found in the recent review by Durham and Hayes[2] and the article by Gershon and Shaw.

Each of the subjects represented in this report experienced many of these acute symptoms during their active periods as agricultural pilots. Case 2 in particular recounts many episodes of nausea, retching, vomiting and abdominal cramps, and the muscular weakness which indicates an advanced stage of acute toxicity. Case 1 was reported at one time to have experienced anginal pain; but this may well have been identical with the sensation of "tightness" in the chest of which the second subject complained. Atropine is an effective antidote against the majority of these acute effects, a

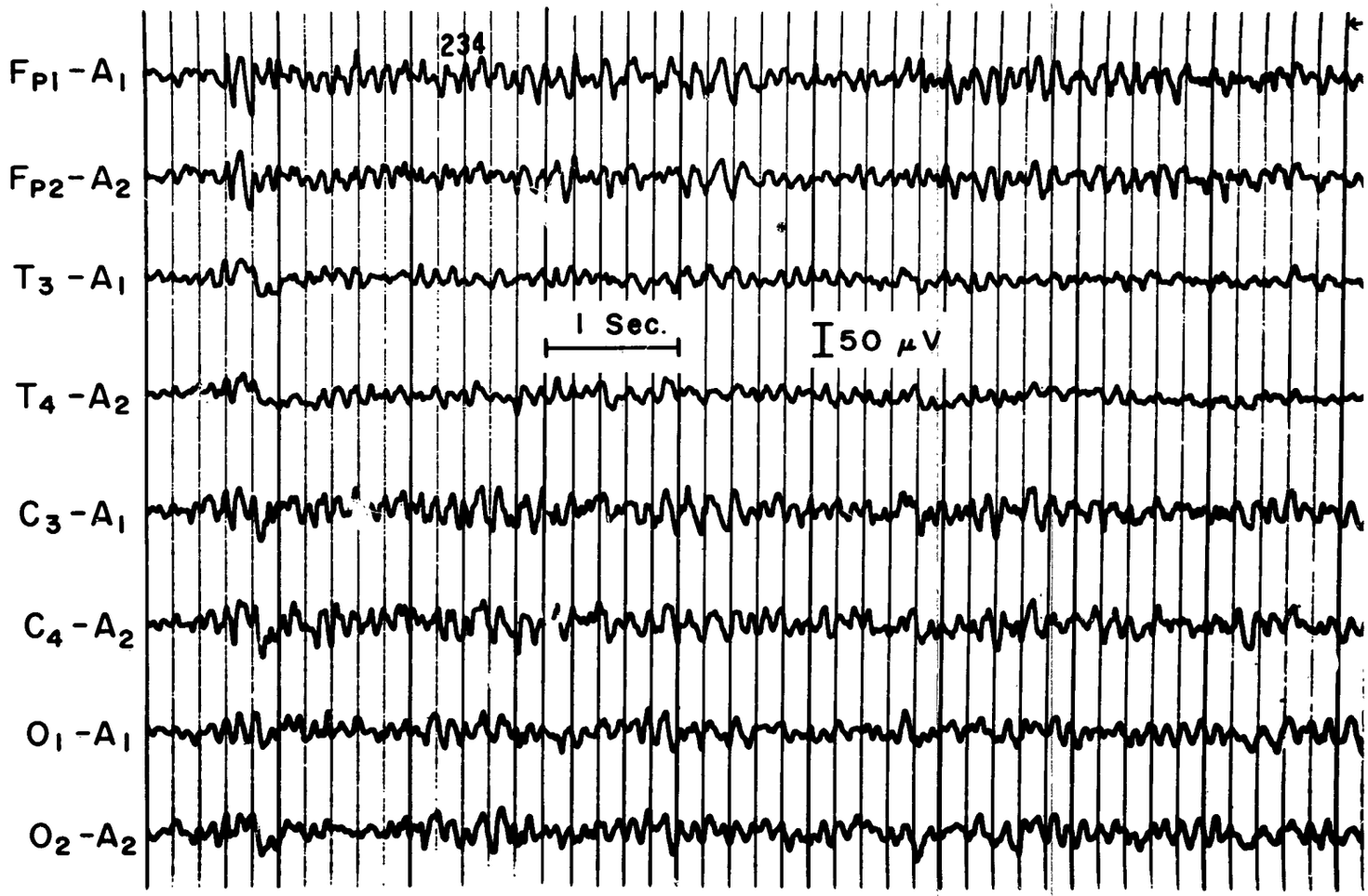

FIGURE 1. Resting EEG showing paroxysmal 5-7 per second slow waves and occasional high voltage bursts (above 100 μV) in leads F_{P_1}, F_{P_2}, C_3, and C_4.

major exception being the initial tremor and later weakness of skeletal muscle.

With or without treatment, the acute signs and symptoms usually subside within one to six days although the activity of both plasma and red blood cell cholinesterase may still be low. It is also true that repeated exposures to small doses of cholinesterase inhibitors may reduce enzyme activity to a low level without the appearance of acute symptoms. The mechanism of adaptation to low levels of enzyme activity is not known.

The nature of the central nervous system symptoms depends upon the manner and degree of exposure. Acute poisoning has been reported to produce ataxia with stumbling gait, headache, restlessness, irritability, impaired ability to concentrate, depersonalization, indifference to environment, wild dreams, slurred speech, tremor, convulsions, medullary-center depression with dyspnea, cyanosis, coma and high-voltage, low-frequency electroencephalographic waves which are more pronounced after hyperventilation.

Since both of our cases are typical of chronic exposure, it is not surprising that neither of them presented an appreciable number of these symptoms at any time. Only headache was prominent in Case 1, and Case 2 showed only irritability, ataxia and slow EEG waves which were of moderate amplitude and not appreciably altered by hyperventilation.

Chronic exposure is associated with anxiety, uneasiness, giddiness, insomnia, somnambulism, lassitude, drowsiness, tinnitus, nystagmus, dizziness, pyrexia, paralysis, paresthesias, polyneuritis, mental confusion, emotional lability, depression with weeping, schizophrenic reaction, dissociation, fugue, inability to get along with family and friends, and poor work performance.

Of these, Case 1 presented the symptoms of anxiety, uneasiness, and depression with weeping. Case 2 complained of dizziness, anxiety, emotional lability, frequent and severe disagreemeents with family and associates and an inability to perform familiar tasks.

Since only close questioning of a non-medically-trained individual would reveal the occurrence of certain of these symptoms, particularly if they were transient, it is possible that some may have been missed in these histories.

Other reports have stated that recovery from schizophrenic and depressive symptoms requires from six to twelve months following removal from further contact with the toxic agents. Sufficient recovery for discharge from medical observation occurred in ten months in our Case 1, but commercial flying was not attempted for another two years. Symptoms which prevent commercial flying still persist in the second pilot six months after his last exposure. Symptoms that persist after 90 to 120 days cannot be associated with low cholinesterase levels in the brain. There is some indication in these and other histories that recovery may be a relative term and a degree of recovery which would permit the resumption of one occupation might not permit the resumption of another.

The EEG pattern found in the second pilot (Fig. 1) is not inconsistent with the findings of other authors[4,6,7] despite lower amplitude and the absence of changes with hyperventilation. The principal difference concerns the duration of the effects, which are reported in other studies as seven days,[4] eleven to eighteen days,[5] and four weeks[3]. If the EEG changes observed here are indeed residual from organophosphate exposure, their persistence exceeds six months. Since experts differ in their interpretation of slow-wave activity, it is not certain whether the EEG obtained one year earlier and pronounced normal was different from the current one.

In the light of present knowledge, it must be considered more likely that the mild liver damage found in both pilots was caused by the chlorinated hydrocarbons to which they were also chronically exposed.

It is interesting to speculate that our cases were the victims of a combination of circumstances almost perfectly designed to produce their central nervous system involvement. They operated in regions with long growing seasons. The nature of the crops and the insect pests demanded the use of organophosphate insecticides. Prolonged periods of good weather and a great demand for their services led to long, uninterrupted periods of flying. All of these factors combined to cause continuous contact with the toxic materials for protracted periods, and encouraged the practice, common among agricultural pilots, of suppressing acute symp-

toms with atropine and continuing their work. In the meantime, the more insidious central nervous effects were developing.

These circumstances are not unique, and it is almost certain that more such cases will appear. Physicians in Latin America and the agricultural regions of the United States are becoming alert to the acute peripheral signs and symptoms of organophosphate toxicity, and recognize them readily. It is now apparent that they must be watchful for central nervous system symptoms as well. They should be especially emphatic in warning pilots to avoid the prolonged, chronic exposure which may lead to psychiatric difficulties.

The case of the second pilot of this report indicates that it is scarcely possible to take excessive precautions against such exposure, since he customarily used a respirator which he kept in good condition, had flown a closed-cockpit aircraft since 1959 and was careful about the cleanliness of both his aircraft and his person.

Even this need not be surprising. Of 23 subjects in one study,[4] all of whom used carbon-filter respirators and wore rubber gauntlets and coveralls, 18 had mild to moderate symptoms, four had severe symptoms but recovered, and one died.

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